

**Experiment Number:** C96019

**Route:** Dosed Water, Dosed Water and Gavage Challenge, Gavage, IV

**Species/Strain:** Rat/F344

**Toxicokinetics Data Summary**  
**Test Compound:** Bromochloroacetic Acid  
**CAS Number:** 5589-96-8

**Date Report Requested:** 02/06/2017

**Time Report Requested:** 17:12:55

**Lab:** Battelle Columbus

Male																		
	Treatment Groups (mg/kg)																	
	2.88 a, #, 2			2.88 b, #, 1			10 c, #, 3			28.8 a, #, 2			28.8 d, #, 1			40 e, #, 3		
	Plasma																	
C <sub>max</sub> (pred) (ug/mL)	0.248	±	0.025				0.475	±	0.031	10.7	±	0.7				6.74	±	0.33
T <sub>max</sub> (pred) (min)	14.2	±	4.0				21.9	±	1.9	29.4	±	3.0				53.2	±	2.6
C <sub>max</sub> (obs) (ug/mL)				0.0801											2.66			
T <sub>max</sub> (obs) (hour)				24											24			
Lambdaz (min^-1)																		
t <sub>1/2</sub> (min)																		
t <sub>1/2</sub> (Alpha) (min)																		
t <sub>1/2</sub> (Beta) (min)																		
k <sub>01</sub> (min^-1)	0.224	±	0.115				0.0457	±	0.0039	0.0709	±	0.0138				0.0188	±	9.0E-4
t <sub>1/2</sub> (k01) (min)	3.09	±	1.58				15.2	±	1.3	9.78	±	1.90				36.9	±	1.8
k <sub>10</sub> (min^-1)	0.0107	±	0.0058				0.0457	±	0.0039	0.0128	±	0.0010				0.0188	±	9.0E-4
t <sub>1/2</sub> (k10) (min)	64.8	±	35.3				15.2	±	1.3	54.1	±	4.3				36.9	±	1.8
k <sub>12</sub> (min^-1)																		
k <sub>21</sub> (min^-1)																		
Cl (mL/min/kg)																		
Cl <sub>1</sub> (mL/min/kg)																		
Cl <sub>1(F)</sub> (mL/min/kg)	107	±	41				354	±	37	23.6	±	1.4				41.0	±	2.5
V <sub>1</sub> (mL/kg)																		
V <sub>2</sub> (mL/kg)																		
V <sub>1(F)</sub> (mL/kg)	9990	±	1890				7750	±	510	1840	±	210				2180	±	110
MRT (min)																		
AUC <sub>0-t</sub> (ug/mL*min)	9.56						25.5			1200						1090		
AUC <sub>inf</sub> (ug/mL*min)	26.9	±	10.3				28.2	±	3.0	1220	±	70				976	±	61

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**Lab:** Battelle Columbus

Male																
	Treatment Groups (mg/kg)															
	57.6 a, #, 2		57.6 d, #, 1		100 h, #, 3		10 IV f, o, 4		10 IV g, *, 4		10 IV i, #, 4		80 IV j, #, 4			
	Plasma															
C <sub>max(pred)</sub> (ug/mL)	25.4	±	5.7			28.1 ±	1.9			21.6	±	5.4		20.2	±	2.1
T <sub>max(pred)</sub> (min)	21.0	±	11.1			61.4 ±	3.4									
C <sub>max(obs)</sub> (ug/mL)				5.17												
T <sub>max(obs)</sub> (hour)				24												
Lambdaz (min^-1)								0.236								
t <sub>1/2</sub> (min)								2.94								
t <sub>1/2</sub> (Alpha) (min)										1.96	±	0.76				
t <sub>1/2</sub> (Beta) (min)										9.48	±	0.51				
k <sub>01</sub> (min^-1)	0.145	±	0.114			0.0163 ±	9.0E-4									
t <sub>1/2</sub> (k <sub>01</sub> ) (min)	4.78	±	3.76			42.5 ±	2.3						5.86	±	0.25	
k <sub>10</sub> (min^-1)	0.00814 ±		0.00170			0.0163 ±	9.0E-4			0.156 ±	0.033		0.118 ±	0.005		0.0260
t <sub>1/2</sub> (k <sub>10</sub> ) (min)	85.2	±	17.7			42.5 ±	2.3			4.46	±	0.96				
k <sub>12</sub> (min^-1)										0.105 ±	0.072					
k <sub>21</sub> (min^-1)										0.166 ±	0.044					
Cl (mL/min/kg)								126					58.5	±	4.6	
Cl <sub>1</sub> (mL/min/kg)										71.9	±	4.3				
Cl <sub>1(F)</sub> (mL/min/kg)	15.6	±	2.9			21.3 ±	1.8									
V <sub>1</sub> (mL/kg)								534		462	±	116		494	±	52
V <sub>2</sub> (mL/kg)										291	±	75				
V <sub>1(F)</sub> (mL/kg)	1910		± 570			1310	± 90									
MRT (min)								3.10		10.5	±	0.5		8.46	±	0.36
AUC <sub>0-t</sub> (ug/mL*min)	3770					4920		79.0		143						
AUC <sub>inf</sub> (ug/mL*min)	3700		± 700			4690	± 390	79.4		139	±	8		171	±	13

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## Toxicokinetics Data Summary

Test Compound: Bromochloroacetic Acid

CAS Number: 5589-96-8

Date Report Requested: 02/06/2017

Time Report Requested: 17:12:55

Lab: Battelle Columbus

Female																		
	Treatment Groups (mg/kg)																	
	2.74 <sup>a</sup> , #, 2			2.74 <sup>b</sup> , #, 1			10 <sup>k</sup> , #, 3			27.4 <sup>a</sup> , #, 2			27.4 <sup>d</sup> , #, 1			40 <sup>l</sup> , #, 3		
	Plasma																	
C <sub>max</sub> (pred) (ug/mL)	0.412	±	0.026				0.599	±	0.026	12.9	±	1.5				11.6	±	0.7
T <sub>max</sub> (pred) (min)	15.4	±	1.6				17.8	±	1.1	23.5	±	4.8				45.4	±	2.6
C <sub>max</sub> (obs) (ug/mL)				0.189									3.84					
T <sub>max</sub> (obs) (hour)				24									15					
Lambdaz (min <sup>-1</sup> )																		
t <sub>1/2</sub> (min)																		
t <sub>1/2</sub> (Alpha) (min)																		
t <sub>1/2</sub> (Beta) (min)																		
k <sub>01</sub> (min <sup>-1</sup> )	0.154	±	0.038				0.0560	±	0.0035	0.102	±	0.036				0.0220	±	0.0013
t <sub>1/2</sub> (k <sub>01</sub> ) (min)	4.49	±	1.10				12.4	±	0.8	6.82	±	2.40				31.5	±	1.8
k <sub>10</sub> (min <sup>-1</sup> )	0.0193	±	0.0047				0.0560	±	0.0035	0.0125	±	0.0015				0.0220	±	0.0013
t <sub>1/2</sub> (k <sub>10</sub> ) (min)	36.0	±	8.8				12.4	±	0.8	55.5	±	6.7				31.5	±	1.8
k <sub>12</sub> (min <sup>-1</sup> )																		
k <sub>21</sub> (min <sup>-1</sup> )																		
Cl (mL/min/kg)																		
Cl <sub>1</sub> (mL/min/kg)																		
Cl <sub>1(F)</sub> (mL/min/kg)	95.3	±	11.9				344	±	26	19.8	±	1.9				27.9	±	2.1
V <sub>1</sub> (mL/kg)																		
V <sub>2</sub> (mL/kg)																		
V <sub>1(F)</sub> (mL/kg)	4940	±	710				6140	±	270	1590	±	280				1270	±	80
MRT (min)																		
AUC <sub>0-t</sub> (ug/mL*min)	17.5						33.0			1260						1290		
AUC <sub>inf</sub> (ug/mL*min)	28.7	±	3.6				29.1	±	2.2	1380	±	130				1430	±	110

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Date Report Requested: 02/06/2017

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Lab: Battelle Columbus

Female																						
	Treatment Groups (mg/kg)																					
	54.9 a, #, 2			54.9 d, #, 1			100 l, #, 3			10 IV f, o, 4			10 IV g, *, 4			10 IV i, #, 4			80 IV j, #, 4			
	Plasma																					
C <sub>max(pred)</sub> (ug/mL)	31.5	±	3.4				44.7	±	3.0				13.5	±	1.0		25.6	±	3.2			
T <sub>max(pred)</sub> (min)	23.7	±	4.9				58.0	±	3.3													
C <sub>max(obs)</sub> (ug/mL)						7.36																
T <sub>max(obs)</sub> (hour)						24																
Lambdaz (min^-1)											0.314											
t <sub>1/2</sub> (min)											2.21											
t <sub>1/2(Alpha)</sub> (min)													4.99	±	0.50							
t <sub>1/2(Beta)</sub> (min)													13.7	±	3.9							
k <sub>01</sub> (min^-1)	0.111	±	0.036				0.0172	±	0.0010													
t <sub>1/2(k01)</sub> (min)	6.27	±	2.06				40.2	±	2.3								5.54	±	0.27			
k <sub>10</sub> (min^-1)	0.0103	±	9.0E-4				0.0172	±	0.0010				0.126	±	0.007		0.125	±	0.006			0.0279
t <sub>1/2(k10)</sub> (min)	67.3	±	5.7				40.2	±	2.3				5.52	±	0.30							
k <sub>12</sub> (min^-1)													0.00795	±	0.00352							
k <sub>21</sub> (min^-1)													0.0562	±	0.0189							
Cl (mL/min/kg)										206							48.7	±	4.7			
Cl <sub>1</sub> (mL/min/kg)													92.9	±	3.4							
Cl <sub>1(F)</sub> (mL/min/kg)	14.1	±	1.4				14.2	±	1.2													
V <sub>1</sub> (mL/kg)										656			739	±	54		390	±	49			
V <sub>2</sub> (mL/kg)													105	±	16							
V <sub>1(F)</sub> (mL/kg)	1370	±	200				822	±	56													
MRT (min)										2.57			9.08	±	0.35		8.00	±	0.39			
AUC <sub>0-t</sub> (ug/mL*min)	3660						5600			46.7												
AUC <sub>inf</sub> (ug/mL*min)	3900	±	380				7050	±	600	48.5			108	±	4		205	±	20			

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LEGEND

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Data are displayed as mean  $\pm$  SEM

MODELING METHOD & BEST FIT MODEL

<sup>a</sup> WinNonlin, version 4.0, 5.0, or 5.0.1, Pharsight Corporation, Mountain View, CA; One-compartment model with first order absorption and elimination. Parameter estimates and SEM are reported to three significant figures.

<sup>b</sup> WinNonlin, version 4.0, 5.0, or 5.0.1, Pharsight Corporation, Mountain View, CA; No kinetic modeling was possible for the non-challenge group animals. Almost all the BCA plasma concentration values were BLOQ of 0.0750 ug/mL. GXA and OXA plasma concentrations were BLOQ or not detected.

<sup>c</sup> WinNonlin Pharsight Corp; One-compartment model with equal first order absorption and elimination no weighting. Model 5 where  $k_a$  equals  $k_e$  (a one-compartment model with equal first order absorption and elimination). Parameter estimates and SEM are reported to three significant figures. GXA and OXA plasma concentration time point data were not presented because all values were BLOQ (4.209 ug/mL GXA and 4.192 ug/mL OXA).

<sup>d</sup> WinNonlin, version 4.0, 5.0, or 5.0.1, Pharsight Corporation, Mountain View, CA; No extensive TK analysis was performed for the non-challenge group data, however, non-compartmental analysis was used to determine  $C_{max}$  and AUC values for the mid and high dose BCA groups for the purpose of examining dose proportionality. No kinetic modeling was possible for the non-challenge group animals for GXA and OXA. The plasma concentrations of GXA and OXA were either BLOQ (4.349 and 4.169 ug/mL, respectively), or not detected, for all dosage groups.

<sup>e</sup> WinNonlin Pharsight Corp; One-compartment model with equal first order absorption and elimination 1/Y weighting. Model 5 where  $k_a$  equals  $k_e$  (a one-compartment model with equal first order absorption and elimination). Parameter estimates and SEM are reported to three significant figures. GXA and OXA plasma concentration time point data were not presented because all values were BLOQ (4.209 ug/mL GXA and 4.192 ug/mL OXA).

<sup>f</sup> WinNonlin Pharsight Corp; Noncompartmental analysis using the mean plasma concentration time. The BCA minus isomer was eliminated much faster than BCA plus isomer for rats and mice.

<sup>g</sup> WinNonlin Pharsight Corp; Two-compartment model with bolus input, first order output, and 1/Yhat2 weighting. The BCA minus isomer was eliminated much faster than BCA plus isomer for rats and mice.

<sup>h</sup> WinNonlin Pharsight Corp; One-compartment model with equal first order absorption and elimination 1/Yhat weighting. Model 5 where  $k_a$  equals  $k_e$  (a one-compartment model with equal first order absorption and elimination). Parameter estimates and SEM are reported to three significant figures. GXA and OXA plasma concentration time point data were not presented because all values were BLOQ (4.209 ug/mL GXA and 4.192 ug/mL OXA).

<sup>i</sup> WinNonlin Pharsight Corp; one-compartment model with bolus input, first order output, and 1/Yhat2 weighting. Parameter estimates are reported to three significant figures.

<sup>j</sup> Graphical Analysis; For the 80 mg/kg IV male and female rat groups, the partial BCA plasma concentration time data was evaluated using graphical analysis.

<sup>k</sup> WinNonlin Pharsight Corp; One-compartment model with equal first order absorption and elimination no weighting. Model 5 where  $k_a$  equals  $k_e$  (a one-compartment model with equal first order absorption and elimination). Parameter estimates and SEM are reported to three significant figures. GXA and OXA plasma concentration time point data were not presented because all values were BLOQ (4.209 ug/mL GXA and 4.192 ug/mL OXA).

<sup>l</sup> WinNonlin Pharsight Corp; One-compartment model with equal first order absorption and elimination and 1/Yhat weighting. Model 5 where  $k_a$  equals  $k_e$  (a one-compartment model with equal first order absorption and elimination). Parameter estimates and SEM are reported to three significant figures. GXA and OXA plasma concentration time point data were not presented because all values were BLOQ (4.209 ug/mL GXA and 4.192 ug/mL OXA).

ANALYTE

# Bromochloroacetic acid

\* Bromochloroacetic acid plus isomer

<sup>o</sup> Bromochloroacetic acid minus isomer

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#### ROUTE & DOSING

<sup>1</sup> Dosed Water: Animals exposed by drinking water ad libitum

<sup>2</sup> Dosed Water and Gavage Challenge: Animals exposed by drinking water ad libitum and by a single gavage administration on Study day 15

<sup>3</sup> Gavage: Animals were administered a single gavage dose

<sup>4</sup> IV: Animals were given a single bolus intravenous injection

#### TK PARAMETERS

$C_{max}$  = Observed or Predicted Maximum plasma (or tissue) concentration

$T_{max}$  = Time at which  $C_{max}$  predicted or observed occurs

$\lambda_{dz}$  = Non-compartmental analysis (NCA) terminal elimination rate constant, NCA  $k_e$  or  $k_{elim}$

$t_{1/2}$  =  $\lambda_{dz}$  half-life,  $t_{1/2}$ , the terminal elimination half-life based on non-compartmental analysis

$t_{1/2}(\alpha)$  = Half-life for the alpha phase

$t_{1/2}(\beta)$  = Half-life for the beta phase

$k_{01}$  = Absorption rate constant,  $k_a$

$t_{1/2}(k_{01})$  = Half-life of the absorption process to the central compartment

$k_{10}$  = Elimination rate constant from the central compartment also  $k_e$  or  $k_{elim}$

$t_{1/2}(k_{10})$  = Half-life for the elimination process from the central compartment

$k_{12}$  = Distribution rate constant from first to second compartment etc.

$k_{21}$  = Distribution rate constant from second to first compartment etc.

Cl = Clearance, includes total clearance

$Cl_1$  = Clearance of central compartment,  $Cl_{app}$  or apparent clearance for intravenous groups

$Cl_{1(F)}$  = Apparent clearance of the central compartment, also  $Cl_{(F)}$  for gavage groups in non-compartmental model

$V_1$  = Volume of distribution of the central compartment, includes  $V_d$  and  $V_{volume}$  of distribution,  $V_z$  apparent volume of distribution NCA,  $V_{app}$  apparent volume of distribution for intravenous studies

$V_2$  = Volume of distribution for the peripheral compartment

$V_{1(F)}$  = Apparent volume of distribution for the central compartment includes  $V_{d(F)}$ ,  $V_{(F)}$  for oral groups, and  $V_{c(F)}$

MRT = Mean residence time

$AUC_{0-t}$  = Area under the plasma concentration versus time curve, AUC, from time  $t_i$  (initial) to  $t_f$  (final),  $AUC_{last}$

$AUC_{inf}$  = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity

**\*\* END OF REPORT \*\***